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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/851,738	05/09/2001	Thomas R. Coolidge	P03660US5	4849

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EXAMINER	
LIU, SAMUEL W	
ART UNIT	**PAPER NUMBER**
1653	

DATE MAILED: 03/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/851,738	COOLIDGE ET AL.	
	Examiner	Art Unit	
	Samuel W Liu	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 December 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-22 and 24-33* is/are pending in the application.

4a) Of the above claim(s) *none* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-22 and 24-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12-1-03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the claims

Claims 14-22 and 24-33 are pending.

Applicants' amendment filed 1 December 2003, which amends claim 14-15, 17-18 and 20-22, adds claims 24-33, and cancels claim 23 has been entered. Note that claims 1-13 were previously canceled by applicants' amendment filed 7 May 2003.

The terminal disclaimer filed 1 December 2003 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of prior US Pat. Nos: 6284725 and 6429197 has been reviewed and is accepted. The terminal disclaimer has been recorded.

The following Office Action is applicable to the pending claims 14-22 and 24-33.

Please note that grounds of objection and/or rejection not explicitly restated and/or set forth below are withdrawn.

IDS

The references lists in IDS filed 1 December 2003 have been considered.

Claim Rejections - 35 USC § 112, the first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 32-33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one

skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification as originally filed does not provide support for the invention as now claimed.

This is a New Matter rejection for the following reasons:

The newly added claims 32, the recitation "the method of claim 24, further comprising reducing an inflammatory response", and newly added claim 33, the recitation "the method of claim 14, further comprising reducing an inflammatory response", represent a departure from the specification and the claims as originally filed.

Applicant's amendment filed 1 December 2003 asserts that no new matter has been added and points to the specification at page 10, the 2nd paragraph, asserts that the support for claims 32 and 33 limitations set forth *supra* can be found in pages 14-16 (see the response, page 10). However, nowhere does in the indicated specification provide a clear support of the above-stated claim recitations, i.e., "further comprising reducing an inflammatory response". The instant claims now recite limitations which were not clearly disclosed in the specification and claims as filed, and now change the scope of the instant disclosure as filed. Such limitations recited in the present claims, which did not appear in the specification or original claims, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Claims 14-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants have not taught a method of preventing decrease in normal function of ischemic and reperfused tissue comprising administering to a subject a pharmaceutical composition comprising (i) a compound that binds to GLP-1 receptor (see claim 14 and dependent claims thereto), or (ii) any exendin peptide (note that the exendin *per se* is genus encompassing exendin 1, 2, 3, and 4) (see claim 24 and dependent claims thereto), or (iii) a compound that is an exendin derivative (see claim 24 and dependent claims thereto), or (iv) a GLP-1 analog (see claim 15). Thus, Applicants are not in possession of the claimed method indicated above.

Applicants have not taught a method of preventing decrease in normal function of ischemic and reperfused tissue comprising administering to a subject a pharmaceutical composition comprising the above-mentioned the composition of (i) or (ii) or (ii), and a method of the same further comprising reducing an inflammatory response (see claims 32-33). Thus, Applicants are not in possession of the claimed method indicated above.

Application has disclosed only ameliorating a tissue damage associated with ischemia-reperfusion using GLP-1, but not the method thereof using any GLP-1 analog encompassing a compound that binds to GLP-1 receptor or is an exendin derivative because the instant disclosure does NOT describe said method. The skilled artisan, therefore, cannot envision all the GLP-1 analog possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent

Application Under the 35 U.S.C.112, ¶ 1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, *i.e.*, structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of the compound that binds to GLP-1 receptor, the GLP-1 analog or/and the exendin derivatives including peptide mimetics, and fails to describe their receptor activities, e.g., stimulate insulin release and inhibit glucagon secretion (note that these activities underline GLP-1 therapeutic potential in the management of ischemia-reperfusion (see [0026]), and fails to provide written description regarding their therapeutic use for ameliorating a condition that is a tissue damage (function decrease of a tissue) associated with ischemia-reperfusion. Thus, applicants were not in a possession of making or/and using any compound that binds with GLP-1 receptor GLP-1 analog, exendin derivative, or any exendin peptide (e.g., exendin 1 or 2) for ameliorating said condition, and not in a prosecution of preventing the said condition using the same thereof. *See University of California v. Eli Lilly and co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Claims 14-33 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not reasonably provide an enablement for how to prevent a condition of a tissue damage associates with ischemia-reperfusion (i.e., decrease in normal function of ischemia-associated reperfusion tissue). The instant application provides no animal model or/and insufficient guidance as to prevention of above-stated condition using (i) a compound that binds to GLP-1 receptor, or (ii) any exendin peptide, or (iii) a compound that is an exendin derivative or (iv) a GLP-1 analog. Given that the claimed method involves the GLP-1 receptor, since agonism or antagonism to the GLP-1 receptor for the methods thereof has not been described in the specification, the outcome of the prevention thereof is highly unpredictable. Thus, the skilled artisan cannot envision consequence of preventing said condition. As result, conception cannot be achieved until a representative description of preventing the condition of tissue damage associated with ischemia-reperfusion has occurred, regardless of the complexity or simplicity of the method. Adequate description requires more than a mere statement that it is part of the invention see *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993).

Also, the specification fails to provide sufficient description regarding how to make and use a compound that binds to GLP-1 receptor. Note that the claimed compound encompasses a large number of organic, inorganic and polymer including modified biopolymer (e.g.,

phosphorylated, or glycosylated, or lipidated or ubiquitinated biopolymer). The organic compound that is non-peptide called T-0632 having high affinity for GLP-1 receptor (see Tibaduiza, E. C. et al. (2001) *J. Boil. Chem.* 276, 37787-37793) is such an example. Yet, the specification provides no guidance or working examples in this regard. Also note that both agonist and antagonist bind to GLP-1 receptor. Without describing whether the compound is agonist or antagonist to GLP-1 receptor, the skilled artisan would have not known biological function of the said compound; thus, the skilled artisan is not in possession of the claimed method of using said compound. Thus, the instant disclosure does not enable the skilled artisan to have possession of the claimed invention as to making and using the above-stated compound.

In addition, the specification fails to provide sufficient description regarding how to use (i) a compound that binds to GLP-1 receptor, or (ii) any exendin peptide, or (iii) a compound that is an exendin derivative or (iv) a GLP-1 analog GLP-1 or analog thereof, or, exendin or derivative thereof, for ameliorating the said condition.

Since the specification does not describe core motif(s) or sequence(s) which is critical role for activity of said analog. Thus, the skilled artisan cannot envision all possibilities of interaction of the analog with GLP-1 receptor and has activities of intact GLP-1, e.g., stimulate insulin release and inhibit glucagon secretion (see [0026]).

The specification is silent in teaching how to make and use a compound derived from exendin (i.e., an exendin derivative). Please note that the term "exendin" encompasses exendin 1, exendin 2, exendin 3 and exendin 4, wherein helospectin is exendin-1; helodermin is exendin-2 (see Table 1). Art in record has taught that only exendin-3 and 4 possess (A) GLP-1 like insulinotropic activity and (B) activity of suppressing plasma free fatty acid (FFA) (see US Pat.

No.5424286). It has not been found that exendin-1 or exendin-2 has the same activities thereof, absent factual indicia to the contrary. Thus, applicants are not in possession of the claimed method using any exendin peptide (exendin 1 or 2) and any exendin derivative. The said derivative (a genus) encompasses numerous mutants and chemical modified forms of exendin. The current disclosure is silent in describing how to make and use the derivative thereof. Thus, applicants are not in possession of the claimed methods using the exendin derivative thereof.

Furthermore, GLP-1 analog and exendin derivative should include agonist and antagonist to GLP-1 receptor. Yet, there is insufficient teaching or direction regarding use of the agonist or the antagonist for the above-mentioned methods. Note that, in pharmacology, agonist and antagonist have opposite effect. Thus, identification of agonist or antagonist is required for sufficient description of GLP-1 analog or exendin derivative when administered to the subject according to the claimed methods.

Therefore, the current application does not provide enablement for making and using (including use in preventing a condition of a tissue damage associates with ischemia-reperfusion) any GLP-1 analog, or any compound that bonds with GLP-1 receptor, or any exendin derivative.

Applicants' response to the rejection under 35 USC 112, the first paragraph

The response filed 1 December 2003 asserts that there is sufficient description and guidance for the skilled artisan to use GLP-1 analog (see page 11, the 2nd paragraph) and for the claimed method of ameliorating a decrease in a function of a ischemia-reperfusion tissue comprising administering to subject a compound that binds with GLP-1 receptor (see page 11, the last paragraph). The applicants' argument is not persuasive because of the reasons stated

above and the followings. First, GLP-1 analog and exendin derivative should include agonist and antagonist to GLP-1 receptor. The specification does not describe or provide guidance as to any GLP-1 analog agonist or antagonist. Yet, there is insufficient teaching or direction regarding use of the agonist or the antagonist for the above-mentioned methods. Note that, in pharmacology, agonist and antagonist have opposite effect. Thus, identification of agonist or antagonist is required for sufficient description of GLP-1 analog or exendin derivative when administered to the subject according to the claimed methods. Second, the claimed "a compound" encompasses a large number of organic, inorganic and polymer including biopolymer (e.g., phosphorylated, or glycosylated, or lipidated or ubiquitinated or other modified form). The non-peptide compound T-0632 that binds with high affinity to GLP-1 receptor (see Tibaduiza, E. C. et al. (2001) *J. Boil. Chem.* 276, 37787-37793) is such the example.

Claim Rejections - 35 USC § 112, the second paragraph

Claims 14-22 and 24-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 14 recites "a decrease in a function of a tissue"; the recitation is unclear as to what said function is". Also, claim 14 does not make it clear as to what is consequence (*agonism* or *antagonism*) of "a compound" binding to GLP-1 receptor. See also claim 24. The dependent claims are also rejected.

Claim 16 recites a Markush group which contains broad term, e.g., "combinations thereof" and also narrow term, e.g., saline, buffered saline, dextrose, water, ethanol, lactose,

phosphate, mannitol, arginine, treholose" A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See also claim 26.

Claim 17 is indefinite because "treatment" is unclear; to what the said treatment is directed?

Claim 20 is indefinite in "infusion" because it appears that the subject for said infusion is missing in the claim; is it infusion of any compound, or GLP-1 infusion, or infusion of a GLP-1 analog ?

Claim 24 recites "a compound derived therefrom"; the term "compound" is indefinite because the specification does not define said "compound". Does the compound refer to an organic or inorganic compound that is covalently conjugated to or coordinated by an exendin peptide, or a biopolymer modified exendin-like molecule? The dependent claims are also rejected.

Claim 32 recites "comprising reducing an inflammatory response"; the recitation is indefinite because the "reducing an inflammatory response" does not constitute an actual step of the claimed method of claim 24 from which claim 32 depends. Note that the "reducing an inflammatory response" *per se* is a process not a step.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is 571-272-0949. The examiner can normally be reached from 9:00 a.m. to 5:00 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Christopher Low, can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.

Karen Cochrane Carlson Ph.D.

SWL

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER

Samuel Wei Liu, Ph.D.

March 4, 2004